NCI, DCP CHEMOPREVENTION BRANCH
INSTRUCTIONS FOR CLINICAL PROTOCOL DEVELOPMENT:
PHASE I/II CLINICAL TRIALS OF NEW CHEMOPREVENTIVE AGENT

Table of Contents

I. INTRODUCTION

This document details the essential features of protocols for Phase I/II clinical trials of new chemopreventive agents. It is divided into sections which correspond to the required protocol sections. Also included is the recommended language to be incorporated in every Chemoprevention Branch (CB) protocol.

II. PROTOCOL SECTIONS

1.0 COVER SHEET

The cover sheet is the primary source of identifying information for NCI and FDA records systems. Each protocol submitted to the Chemoprevention Branch must have a cover sheet with the items described below.

- Date of protocol document
- Local IRB protocol number
- Title of the protocol
- Principal Investigator (including: name, affiliation, address, telephone number, facsimile number)
- Name and location of the study site(s) or institution(s)
- List of each drug by name (and NSC number, if applicable)

2.0 PROTOCOL SYNOPSIS

See Attachment I.

3.0 TABLE OF CONTENTS

See Attachment II (includes List of Tables, Figures, Appendices).

4.0 OBJECTIVES

Study objectives are concise statements of the major or minor questions that the study is designed to answer. Each objective should be stated as specifically and succinctly as possible in the protocol. It is not suitable to write that the objective is “to determine the mechanism of action of drug X” since this objective is too general, vague and merely restates the overall goal of the study. It is preferable to write that the study objective is to evaluate the effects of a daily dose N of drug E in population X on parameters Y and Z by continuous or daily recording of results obtained in tests A and B during time period C, as compared with drug D at dose E, under the same experimental conditions.

Objectives are usually numbered in order of priority or importance, *e.g.*:

2.1 First OBJECTIVE/HYPOTHESIS
2.2 Second OBJECTIVE/HYPOTHESIS
2.3 Third OBJECTIVE/HYPOTHESIS

5.0 BACKGROUND AND RATIONALE

Sufficient background information should be included so that the rationale for the study is clear. The rationale for selection of the target population, the chemopreventive agent(s), and the study endpoints (*e.g.*, specific surrogate endpoint biomarkers) must be clearly addressed. The choice of particular techniques for endpoint measurement should also be justified. Likewise, any techniques specified for measurement of drugs, metabolites and drug effects should be justified.

6.0 SUMMARY OF STUDY PLAN

The purpose of this section is to provide a brief synopsis of the study so the reader does not have to piece it together independently. This section should include:

- Study design (*e.g.*, double-blind, placebo controlled, multi- or single center, Phase I, II)
- Number of subjects to be enrolled (total and per arm)
- Brief description of the subject population
- Treatment plan which should note the treatment groups and the dose(s) and duration of exposure to study drug
- When the subjects will be assessed
- A description of the measurements that will be taken to meet the objectives of the study
- A description of clinical procedures, lab tests or other measurements to be obtained to monitor the effects of the study drug on human safety and minimize risk.

7.0 SCHEMA

See Attachment III for sample schema.

8.0 SUBJECT SELECTION

8.1 Demographics: The anticipated demographic (*e.g.*, age and gender) make-up of the subjects to be enrolled (*e.g.*, healthy volunteers, persons at increased cancer risk, or subjects with prior cancer diagnosis). The sources or methods of recruitment (*e.g.*, media recruitment, high-risk clinic rosters, hospital cancer registry, or physician

referral). If multiple facilities are participating in the study, all (*e.g.,* centers, clinics or hospitals) should be identified specifically in this section.

8.2 Inclusion Criteria: Specific health, risk, or disease requirements. For healthy volunteers, these may comprise the absence of chronic medical conditions or regular medications; for persons at increased cancer risk, definition of increased risk or method/model for assessing risk; for cancer subjects or subjects with precancerous lesions, histologic confirmation of diagnosis, time from diagnosis, and disease status at entry (stage or extent of disease).

Specific health status requirements (*e.g.,* age, ECOG performance status, life expectancy).

Organ function parameters.

Other eligibility requirements relevant to the chemoprevention study agent or disease process.

8.3 Exclusion Criteria: Specific contraindications to participation based on agent pharmacology and metabolism, toxicology, and/or clinical considerations.

EXAMPLE: Exclusion Criteria:

1. Use of any nonsteroidal antiinflammatory agent within 2 weeks prior to enrollment
2. Participation in another investigational study within 1 month prior to enrollment
3. A history of smoking within 1 month prior to enrollment
4. Active malignancy at any other site.

9.0 TREATMENT

9.1 Name of Drug/Agent

9.2 Dose Groups and Duration of Exposure

9.3 Dose Selection: Describe the method and data supporting the dose(s) to be administered.

9.4 Formulation: Suggested information to include in this sub-section is the type of drug formulation to be used (*e.g.,* oral), formulation number (if available), description of the drug (*e.g.,* gelatin capsules, clear liquid including drug substance content), and a list of ingredients in the vehicle/excipient.

9.5 Administration: Indicate who will administer the drug, how much should be administered, when it should be taken and whether it should be taken with food.

EXAMPLE:	Subject will self administer the drug. They will be instructed to take one capsule orally each day. It should be taken immediately after breakfast.

9.6 Supplier: Indicate who will provide the drug for the study. It is sufficient to note NCI or McKesson Bioservices as the distributor of the drug.

9.7 Packaging and Labels: Describe in detail how the study drug will be packaged. This description should include container(s) (*e.g.*, box, bottle, blister), amount of study drug per container (*e.g.*, two bottles per box with 30 capsules in each bottle), the information noted on the label of each container (*e.g.*, subject ID, study number, distributor) and if blinded, how the label will be constructed to maintain the blind (*e.g.*, three-part occluded label).

9.8 Storage: Instructions regarding the proper storage of the drug at the study site.

EXAMPLE:	The study medication will be stored at room temperature (30°C), protected from environmental extremes and in a locked cabinet or room.

9.9 Dispensing Procedure: Identify the party responsible for dispensing the drug to the subject.

EXAMPLE:	All study personnel except the pharmacist will be blinded to the study drug treatment.

For randomized trials, also describe the procedure for randomizing a subject to a treatment group.

EXAMPLE:	There will be up to ??? groups each consisting of ??? subjects. Following determination of eligibility, each subject will be given a unique subject number and thereby be assigned to a dose group. Subjects in groups ??? will be randomized in a 2:1 ratio to receive drug X or placebo.

9.10 Drug Accountability: Outline in detail the records that the investigator must insure are maintained regarding the receipt, distribution and disposition of the study drug and indicate the party who will be responsible for maintaining such records.

EXAMPLE:	The investigator is required to maintain adequate records of the receipt, dispensing and final disposition of the study drug. This responsibility has been delegated to the ??? Pharmacy. The receipt record (*e.g.,* packing slip) should include from and to whom the study drug was shipped, date, quantity, and batch or lot number. The dispensing record should note the quantities and dates study drug was dispensed to and returned by each subject. At the completion of the investigation, all unused study drug will be returned to the NCI/DCP repository. The record documenting the return of unused drug should include the quantity, date, batch or code, and name of the person or department to whom the drug was returned.

9.11 Dose Reduction: When and how is it appropriate to reduce the dose of study drug during this study?

EXAMPLE:	For grade 1 toxicity or less, no dose modification will be made. For grade 2 toxicity, the dose of study drug will be reduced by 50%. The reduced dose will be maintained for the remainder of the study. For grade 3 or 4 toxicity, therapy will be discontinued until toxicity resolves to grade 1 or less. At that time, the use of study drug will be resumed at 50% of the original dose.

9.12 Unblinding: Obviously, this sub-section is only necessary if the study is blinded.

If so, this sub-section should address the following:

- Procedure for retaining the blind
- Who will be able to break the blind
- Circumstances for breaking the blind
- Procedure for breaking the blind

9.13 Adherence/Compliance

9.13.1 Method: Describe the method(s) that will be utilized to monitor each subject's drug compliance (*e.g.*, medication diaries, pill counts, drug/metabolite plasma levels, and/or drug effect biomarkers).

EXAMPLE: The research staff will evaluate drug compliance using the following means:

1. The subjects will be given a calendar at each clinic visit and instructed to initial it each time a dose is taken.
2. Each subject will be given a bottle containing 30 capsules of study drug at each clinic visit and instructed to return all unused capsules to the investigator. At the end of the treatment period, the actual quantity of unused drug will be compared to the anticipated amount of unused drug and the subject calendar.
3. Each subject's serum drug level will be evaluated over the course of the study.

9.13.2 Definition: Based on compliance, describe which subjects will be included in the statistical analysis (*i.e.*, evaluable based on compliance).

EXAMPLE: All subjects with ≥80% compliance as determined by quantity of unused drug returned to the site and confirmed by pharmacokinetic analysis will be considered evaluable for determining the effect of the study drug.

10.0 CLINICAL EVALUATIONS/PROCEDURES

10.1 Schedule of Events: This is a table which lists the procedures and laboratory evaluations to be performed and when each is to be completed. This table may be submitted in an appendix. Ideally, it will also indicate when each of the CRFs is to be completed. See Attachment IV for example.

10.2 Pre-treatment Procedures: Describe in detail all the procedures that must be completed for a subject before treatment can be initiated.

10.3 On-treatment Evaluations: Indicate when and what procedures are completed while the subject is on treatment.

10.4 End of Treatment Evaluations: Specify the evaluations that must be performed when a subject discontinues use of the study drug.

11.0 LABORATORY EVALUATIONS

11.1 Laboratories: Identify the laboratory(ies) which will be doing each analysis.

11.2 Collection and Handling Procedures: Describe these procedures for each type of sample to be obtained (*e.g.*, biopsy, serum). Possible information to include in this description is amount to be collected, when the sample should be obtained (*e.g.*, fasting, prior to A.M. dose), processing of sample (*e.g.*, details of tissue fixation, embedding, processing and sectioning), labeling of sample, and storage requirements (*e.g.*, frozen at –20EC).

11.3 Shipping Instructions: This sub-section is only necessary if some of the samples must be shipped to an off-site laboratory for analysis. If this is the case, this sub-section should note how the samples should be packaged (*e.g.*, in a polystyrene container surrounded with dry ice), type of carrier to be utilized (*e.g.*, overnight carrier), when the samples can be shipped (*e.g.*, Monday through Wednesday), and the name, address and telephone number of the person to whom the samples are being sent.

12.0 REPORTING ADVERSE EVENTS

(Note: Below are the recommended sub-sections to be included in this section of the protocol along with **recommended language** for each.)

12.1 Definition: An adverse event is any condition which appears or worsens after initiating the use of study drug. All adverse events should be noted on the Adverse Reaction CRF, whether or not it is felt to be related to the study drug.

12.2 Severity: Whenever possible, adverse events will be graded by a numerical score according to the defined Toxicity Grading Scale (NCI's Common Toxicity Criteria) included in Appendix B. [Note: These criteria may be expanded or modified to (a) include agent-specific effects not covered by the criteria (*e.g.,* ocular and dermatologic effects associated with retinoids), and/or (b) further delineate "mild" (grade 1) toxicities which may be relevant to chemoprevention applications (*e.g.,* grade 1 transaminase elevations <2.5 x N), particularly if frequent or persistent. Additional criteria should be included as indicated; when possible, the additional criteria should be consistent with those used in earlier studies of the same or related agents.] Adverse events not included in the defined Toxicity Grading Scale should be scored according to their impact on the subject's ability to perform daily activities as follows:

Mild (causing no limitation of usual activities)	Grade 1
Moderate (causing some limitation of usual activities)	Grade 2
Severe (causing inability to carry out usual activities)	Grade 3
Life-threaatening	Grade 4
Fatal	Grade 5

This effort to assess the grade of an adverse event will be documented by recording the data on the Adverse Reaction CRF.

12.3 Follow-up: (Recommended language: All adverse events, including laboratory abnormalities that in the opinion of the Investigator are adverse events, will be followed up according to good medical practices.)

12.4 Serious Adverse Events: (See Attachment V for form) A serious adverse event is defined (by ICH Guideline E6) as those events, occurring at any dose, which meet any of the following criteria:

- fatal;
- immediately life threatening;
- results in inpatient hospitalization or prolongation of existing hospitalization;
- results in persistent or significant disability/incapacity; or
- results in a congenital anomaly/birth defect

In addition, events that may not meet these criteria, but the investigator thinks are very unusual and/or potentially serious, will also be reported in the same manner as events that do meet the serious adverse event criteria.

Reporting Serious Adverse Events: In the interest of subject safety in this study and to fulfill regulatory requirements, serious adverse events (no matter the apparent relationship to study medication) will be reported to the Sponsor (NCI, DCP, Chemoprevention Branch) immediately.

Any serious adverse event, including any event resulting in death, which occurs during the study must be reported by telephone, within 24 hours of the Investigator learning of the event, to:

Gary J. Kelloff, MD or Medical Monitor (as specified in the contract)
Chemoprevention Branch
DCP/National Cancer Institute/NIH
Phone: (301) 496-8563

A written report will follow within 48 hours of the event to:

Gary J. Kelloff, MD or Medical Monitor (as specified in the contract)
Chemoprevention Branch
DCP/National Cancer Institute/NIH
Executive Plaza North, Suite 201
6130 Executive Blvd., MSC 7322
Bethesda, MD 20892

For Express (*e.g.*, Federal Express, DHL, Airborne) or Hand Delivery
Executive Plaza North, Suite 201
6130 Excecutive Blvd
Rockville, MD 20852

Besides the initial 24-hour telephone report, all serious adverse events must be entered in the Adverse Reaction CRF. Prompt follow up reports of the clinical outcome will be sent to the Sponsor.

13.0 CONCOMITANT MEDICATION:

Indicate any limitations on medications (other than the study drug) while participating in the study.

14.0 "OFF- STUDY" CRITERIA

14.1 Study Termination: Specify the criteria for removing a participant from chemoprevention treatment or from the study protocol. State that NCI, as Sponsor, has the right to discontinue the investigation.

EXAMPLE: The NCI Project Officer can make the decision to terminate the study. This decision could be based on factors such as unacceptable adverse effects, lack of SEB modulation on preliminary analysis, poor accrual, *etc.*

14.2 Premature Termination of a Subject: This sub-section should define premature termination for this study and provide the reasons this may occur.

EXAMPLE: Every effort will be made to keep subjects in the study. However, subjects who do not complete at least ?? days of treatment will be classified as premature terminations.

Possible reasons for premature termination include:

1. Adverse event: The subject develops an adverse event which in the opinion of the subject or investigator warrants termination from the study. A subject will be removed from the study for grade 3 or 4 toxicity which does not respond to discontinuation of therapy.
2. Personal reason: A subject may withdraw from the study at any time.
3. Non-compliance: The subject was inappropriately enrolled or fails to comply with instructions concerning drug administration or clinic visits.
4. Lost to follow-up: Diligent attempts must be made by telephone and letter to determine the circumstances for loss to follow-up, since such loss may be related to the study drug.

Also, NCI may request that the treatment of a particular subject be discontinued.

15.0 DATA MANAGEMENT

15.1 Case Report Form (CRF), Appendix C: Specify the documents on which the following information is to be recorded:

- On-study information, including participant eligibility data and participant history
- Flow sheets or other forms for interim safety and efficacy evaluations
- Specialty forms for surgery, pathology, chemistry, and molecular biology as appropriate
- Off-study and follow-up (if applicable) summary sheets

EXAMPLE:	The CRF is a set of forms for each subject that provide a record of the data generated according to the protocol. These forms are to be completed on an ongoing basis during the study. The medical chart is the source of verification of the data. During the study, the CRF will be monitored for completeness, accuracy, legibility and attention to detail. The CRF will be retained for review.

15.2 Data Entry, Data Management and Quality Control: Suggested information to be discussed in this sub-section:

- Who will complete the CRF?
- Identify the facility responsible for management of the data generated by the study
- Describe the procedure for data entry (*i.e.*, how will the data get from the CRF into the database)
- Describe quality control procedures (*e.g.*, double entry, edit or cross checks)
- Describe the format for submitting the data to NCI
- Provide validation documentation of data management system

15.3 Progress Reports: Based on the Investigator's contract with NCI, state the Investigator's obligations in reporting the progress of the study to NCI.

EXAMPLE:	The Investigator must inform NCI of the progress of the study on a quarterly basis. The NCI progress reporting requirements are provided in Appendix ???.

15.4 Final Report: Based on the Investigator's contract with NCI, state the Investigator's responsibilities concerning the final report after the study is completed.

16.0 CRITERIA FOR EVALUATION AND ENDPOINT DEFINITION

Delineation of study endpoints and methods for measuring or evaluating them are described in this section. For chemoprevention studies, endpoints usually fall into the following categories:

16.1 Efficacy Endpoints: Depending on the study hypotheses and design, efficacy endpoints may include incidence of invasive or preinvasive disease (*e.g.*, polyp incidence); clinical response (*e.g.*, change in number and severity of leukoplakia by physical examination); histologic or cytologic response (*e.g.*, change in severity of dysplasia in biopsy materials); and/or modulation of surrogate endpoint biomarkers (SEBs). Endpoints should be defined clearly. Methods for assessment may be described briefly and referenced in this section, with detailed descriptions of laboratory procedures provided in the Appendices (see Section 20).

16.2 Pharmacokinetics, Safety Studies and Drug Effect Biomarkers: As appropriate, other endpoints (serum/plasma/tissue drug/metabolite levels, other drug effect biomarkers) should be defined clearly. Methods for assessment may be described briefly and referenced in this section with detailed descriptions of laboratory and computer modeling procedures provided in the Appendices (see Section 20).

17.0 STATISTICAL METHODS

This section should include who will be responsible for analyzing the data. An adequate statistical section discusses the study design in relation to the objectives of the study and the plan for the evaluation of the data, specifically:

17.1 Methods for Randomization and Stratification

17.2 Sample Size Justification: The total sample size should be justified for adequate testing of study hypotheses. This should include a- and ß-error levels; differences to be detected for comparative studies; and size of the confidence interval to be constructed around the estimated outcome.

17.3 Evaluability: Criteria for considering a participant "evaluable" in the study analysis; this usually includes considerations of participant adherence/ compliance with the study regimen and of the availability of endpoint information.

17.4 Interim Analyses: Provisions for interim analyses should be included here if relevant to the investigational agent(s) and study design.

17.5 Statistical Analyses: This includes plans for statistical analyses, with clear specification of study hypotheses and primary endpoints.

18.0 ETHICAL AND REGULATORY CONSIDERATIONS

(Note: Below are the sub-sections to be included in this section of the protocol along with **recommended language** for each.)

18.1 FDA Form 1572: The Principal Investigator will sign an investigative statement (FDA Form 1572) prior to initiating this study stating that the study will be conducted in compliance with regulations for clinical investigations.

18.2 IRB: Prior to initiating the study, the Principal Investigator must obtain written approval to conduct the study from the appropriate IRB. Should changes to the study protocol become necessary, protocol amendments will be submitted in writing to the IRB by the Principal Investigator for IRB approval prior to implementation.

18.3 Informed Consent: All potential candidates for the study will be given a copy to read of the Informed Consent for the study (See Appendix ???). The investigator will explain all aspects of the study in lay language and answer all the candidate's questions regarding the study. If the candidate desires to participate in the study, he/she will be asked to sign the Informed Consent. Study drug will not be released to a subject without a signed Informed Consent. Subjects who refuse to participate or who withdraw from the study will be treated without prejudice.

18.4 Outside Monitoring: The FDA and NCI/DCP Chemoprevention Branch or their designees may monitor/audit various aspects of the study. These monitors will be given access to facilities, supplies and records to review and verify data pertinent to this study.

18.5 Record Retention: Clinical records for all subjects studied including history and physical findings, laboratory data, and results of consultations are to be maintained by the Investigator in a secure storage facility. These records are to be stored indefinitely. It is the Investigator's responsibility to retain copies of the completed CRFs until notified in writing by the NCI/DCP Chemoprevention Branch to destroy.

19.0 REFERENCES

20.0 APPENDICES

(Note: The following are the appendices that most protocols should include.)

20.1 Methods for Laboratory Procedures and Clinical Procedures (*e.g.*, Endoscopy, Biopsy) Including Necessary Preparations and Anticipated Risks

20.1.1 Specimen Collection, Handling, Transportation, Storage, and Processing

20.1.2 Drug Levels, Metabolites, and/or Drug Effect Biomarkers

20.1.3 Computer-Assisted Image Analysis and Algorithm Development

20.1.4 Surrogate Endpoint Biomarkers

20.2 NCI Common Toxicity Criteria

20.3 Sample Case Report Form

20.4 Subject Informed Consent

Attachment I
PROTOCOL SYNOPSIS

TITLE OF PROTOCOL:
PROTOCOL IRB NUMBER:
PRINCIPAL INVESTIGATOR:
INSTITUTION (NAME AND ADDRESS):
CO-INVESTIGATORS:
STUDY CENTER(S):

Study Agent(s)	Formulation	Dose	Regimen	Route

Study Design (including phase of development, objectives, diagnosis and main entry criteria):
Methodology (including endpoints, laboratory tests, sample collections):
Study Duration (years):
Proposed Entry Date of First Subject:
Estimated Completion Date of Dosing:
Proposed Accrual Rate (subjects per month):
Duration of Treatment:
Follow up:

Attachment II
Protocol Table of Contents

Attachment III
Sample Schema

Protocol Title

Name of Principal Investigator and Institution

Subject Population (*e.g.,*Women with newly diagnosed CIN III)

9

Randomize to X mg Drug A or placebo qd for 6 months (3-day holiday/month) (25/arm)

9

Summary of Evaluations to be conducted and timepoints (*e.g.,* Repeat colposcopy at 3 months; colposcopy with biopsy at 6 months; pap smears at 3 and 6 months)

9

Summary of Endpoints (*e.g.,* Histological response of CIN; modulation of intermediate biomarkers [DNA content, PCNA, EGFR, RAR])

Attachment IV
Sample Schedule of Events

Evaluation/Procedures	Screening/ Baseline (Day 0)	Day 1	Week 1	Month 1	Month 3	Month 6/ Termination	Early Withdrawal
Informed Consent	X						
On Study Form	X						
Medical History	X						
Physical Exam	X					X	X
Pregnancy Test	X~						
Height/Weight	X	X					
Vital Signs		X	X	X	X	X	X
Serum Chemistry	X			X	X	X	X
Hematology	X			X	X	X	X
Urinalysis	X			X	X	X	X
PK Blood Samples		X				X	
Adverse Events			X	X	X	X	X
Concomitant Medication		X	X	X	X	X	X
Dispense/Record Study Medication		X	X	X	X	X	X
Off Study Form						X	X

~ At risk females only

Adverse Event Reporting Chart: Summary of Investigator's Reporting Obligations to the National Cancer Institute, Division of Cancer Prevention, CB of Adverse Events in Phase I–III Clinical Trials

Reaction	*Reporting Obligation*
a. ALL SERIOUS ADVERSE EVENTS (Fatal, all life-threatening events (Grade 4)[2], any adverse drug experience occurring at any dose that results in the following: inpatient hospitalization or prolongation of existing hospitalization, persistent or significant disability/incapacity, a congenital anomaly/birth defect. Important medical events that may not result in death, be life threatening, or require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgement, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.	REPORT BY PHONE TO CB WITHIN 24 HOURS.[1] (written report to follow within 48 hrs[3])
b. ALL ADVERSE EVENTS (SERIOUS, NON-SERIOUS)[4]	REPORTED in the CRF and Progress Reports.

[1]Telephone number available 24 hours daily: 301-496-8563 (Recorder after hours); FAX: 301-402-0553
[2]Use designated DCT/NCI Common Toxicity Criteria, if applicable.

[3]Report to: **Medical Monitor (as specified in the contract)**
Chemoprevention Branch
DCP/National Cancer Institute/NIH
Executive Plaza North, Suite 201
9000 Rockville Pike
Bethesda, MD 20892
For Express (*e.g.*, Federal Express, DHL, Airborne) or Hand Delivery
Executive Plaza North, Suite 201
6130 Executive Blvd.
Rockville, MD 20852

[4]A list of all known toxicities can be found in the Investigator's Brochure or package insert.

IRB Protocol No._____ Patient No._____

NCI, DCP, CHEMOPREVENTION BRANCH
SERIOUS ADVERSE EVENT FORM

REQUIRED FIELDS ON ALL REPORTS

Today's Date:	Drug under Investigation:	Study (Indication):
Sponsor: NCI, DCP, Chemoprevention Branch		
IND No.:	IRB Protocol No.:	

[ ] Initial [ ] Follow-up	Patient No.: Sex: (circle one) M F Age:	Dose:
Event Onset Date: (Month/Day/Year) Event Approx. Time: (indicate am/pm) Event Place:	Primary Event (diagnosis):	
Duration of Exposure:	Primary Treatment Approx. Time (am/pm): Primary Treatment (to event):	
Attending Physician (Name): Phone/FAX No.: Hospital/Clinic: Address:		
Describe Event (if applicable, include dates of hospitalization for event):		
Form completed by: PI (Print Name) _____ Title _____ PI Signature _____ Date _____ Phone No. _____ (Month/Day/Year)		

IRB Protocol No._____ Patient No._____

ALL FIELDS (A-E) APPEARING IN THE FOLLOWING PAGES MUST BE COMPLETED FOR THE INITIAL REPORT; THEREAFTER, ONLY COMPLETE TO PROVIDE ADDITIONAL/CORRECTIVE INFORMATION.

A. Site information

1. Investigator Name
2. Address

B. Patient Information

1. Patient Initials	2. Date of Birth: _____ (Month/Day/Year)	3. Weight at time of event: _____ [ ] kg [ ] lbs [ ] not available	4. Height at time of event: _____ [ ] cm [ ] ft [ ] not available

C. Suspect Medication(s)

1. Study Design: [ ] Blind [ ] Open/Unblind

>> If open, specify: Dose (*e.g.*, 300 mg) _____ Frequency (*e.g.*, qd) _____ Route _____

2. Study Drug	Formulation (e.g., tablet, solution)
	Lot No. (if known)

3. Start Date of Study Drug (Month/Day/Year):

4. Was Study Drug stopped/interrupted/reduced in response to event? [ ] No [ ] Yes

>> If yes, complete a–e:

a. If stopped, specify date study drug last taken: _____ [ ] NA
(Month/Day/Year)

b. If reduced, specify: New dose _____ Date reduced _____ [ ] NA
(Month/Day/Year)

c. If interrupted, specify total number of days not given: _____ [ ] NA
d. Did event abate after study drug was stopped or dose reduced? [ ] NA [ ] Yes [ ] No
e. Did event reappear after study drug was reintroduced? [ ] NA [ ] Yes [ ] No

5. Was patient taking any other medications concomitantly at the time of the event? [ ] No [ ] Yes >> If yes, complete below.
(DO NOT LIST DRUGS USED TO TREAT EVENT)

Drug Name Doses (units, frequency, route, indication for use)	Start Date			Stop Date or mark (X) if continuing			
	Month	Day	Year	Month	Day	Year	(X)

(continue on a separate sheet if necessary)

IRB Protocol No._____ Patient No._____

D. Adverse Event

1. Relevant Laboratory/Diagnostic Tests [ ] No tests performed

Date			Test	Results	
				Actual Value	Normal Range
Month	Day	Year			

(continue on a separate sheet if necessary)

2. Relevant Medical History, including preexisting conditions (*e.g.*, allergies, race, pregnancy, smoking & alcohol use, hepatic/renal dysfunction, medical/surgical history, *etc.*)

Date (if known)			Diseases/Surgeries/Treatment

(continue on a separate sheet if necessary)

3. **NCI Toxicity GRADE of the event** (use NCI Common Toxicity Criteria): [ ] 1 [ ] 2 [ ] 3 [ ] 4 [ ] 5

4. Why Serious?
[ ] fatal [ ] congenital anomaly/birth defect [ ] new/prolonged hospitalization

[ ] life-threatening

[ ] significant disability/incapacity [ ] other, specify: _____

5. Outcome of Event (at time of report)
[ ] resolved [ ] improved [ ] unchanged [ ] worse [ ] not available

[ ] fatal >>> date of death (Month/Day/Year): _____ Autopsy performed? Y N (circle one)

cause of death: _____ (please attach death certificate and autopsy report, if applicable)

6. Investigator's opinion of the relationship between the event and the study drug (If more than one event is being reported, list secondary events and corresponding relationship to study drug in the comments section below.)

[ ] Present (circle one - possible, probable, definite) [ ] Absent (circle one - none, unlikely)

7. Was this event reported by the investigator to (check all that apply): [ ] IRB [ ] Manufacturer/Distributor
[ ] Other Investigators participating in this study, if checked, please list names and institutions

_____
_____
_____
_____
_____

E. Comments/Clarifications:

FOR NCI USE ONLY

1. Date NCI notified of event (Month/Day/Year): Time:

2. Medical Monitor Review:

Medical Assessment of Event (including drug relationship and expectancy):

Is this an FDA reportable (7-day) event? [ ] Yes [ ] No Date reported:_____

Is this an FDA reportable (15-day) event? [ ] Yes [ ] No Date reported:_____

>> If No, specify reason:_____

Is more information expected? [ ] Yes [ ] No

>> If Yes, specify:_____

Was this event communicated to other NCI contractors using this investigational drug? [ ] Yes [ ] No

>> If Yes, how? By telephone (attach a TC Form): [ ] Yes, attached TC Form [ ] No
Other (FAX, Mail, e-mail, *etc.*): [ ] Yes, attached a copy of the correspondence [ ] No

Medical Monitor: Print name _____ Signature _____ Date _____

Distribution: (circle one, after copying)

NCI Files CCSA Files Monitor/Manager Files

Attachment VI
NCI Progress Reporting Requirements

Progress Report:

[Insert NCI Contract No. and Protocol Title]

Date of Report:

Period Covered:

Principal Investigator:

Principal Co-Investigator(s):

Protocol Number:

IND Number:

Institution(s):

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Prepared by:

Progress Report: [Insert NCI Contract No. and Protocol Title]

Study Purpose:

Study Population:

Treatment Groups and Duration of Drug Exposure:

Study Completion Status:

Number of Subjects/Patients Planned:

Current Enrollment

Number Screened:
Number Enrolled:
Number Currently On Study:
Number Completed:

Number Dropped out

Non-study Related:
Adverse Event Related:

Number of Deaths

Related to Drug Administration:
Unrelated to Drug Administration:

Number of Participants Replaced (if applicable):

Number of Evaluable Participants:

Description of Study Results to Date:

Actions, Dose-Response, and Drug Bioavailability Data:

Protocol Amendments:

Instructions for Completing Table 1: CUMULATIVE ACCRUAL DATA

GENERAL:	Update this table on a monthly or quarterly basis
Patient ID	The study number for the patient, not their hospital record number.
Date of Birth	Use consistent numbering (e.g., Month/Day/Year).
Sex	Either M for male or F for female.
Weight	Include units (e.g., lbs. or kg).
BSA	Body Surface Area if applicable. Define any calculations used to obtain m^2.
Height	Specify units (e.g., cm or inches).
Study Drug Dose	Include dosage, units and frequency (e.g., 200 mg bid).
Date Enrolled	Date (Mon/Day/Yr) patient enrolled into study.
Date Study Drug Started And Stopped	Dates (Mon/Day/Yr) patient received first and last dose on study.
Current Study Status	Patient status at the end of reporting period (i.e., off study, ongoing)
Reason Off Study	If patient off study, specify reason (i.e., completed, due to adverse event, poor compliance, personal reason, etc.)

Protocol Number: _____ **Date:** _____

Instructions for Completing Table 2: LISTING OF ADVERSE EVENTS

General:	Update this table on a monthly or quarterly basis. If information is unavailable, please use --- (dashes) for that particular box.
Patient ID	The study number for the patient not their hospital record number.
Dose at Event	The dose of the study drug the patient was receiving at the time of the event. The unit (e.g., mg) and frequency (e.g., bid) may be specified within the parentheses in the column header or within the table.
Duration of Drug at Event	The number of days, weeks or months patient has received the study drug before experiencing the event.
Event	Describe the event (e.g., nausea, headache, pain in hands, etc.) Do not combine several events unless the events are clearly a syndrome (*e.g.*, cold, flu).
Grade	Determine from the NCI Common Toxicity Criteria or the institution's own scale for events not covered by the NCI criteria. This should be a numerical description (i.e., mild = 1; moderate = 2; severe = 3; life-threatening = 4; fatal = 5.)
Event Start and Stop Date	Specify dates in Month/Day/Year format.
Event Recovery Status	Indicate whether resolved or not resolved.
Relation to Drug	This is the principal investigator's assessment of the relationship between the event and the study drug. The following terms should be used: Unrelated, Unlikely, Possible, Probable, or Definite.
Drop Out Related to Adverse Event	Indicate if the patient dropped out of the study due to this adverse event (Y for Yes or N for No).
SAE Form Filed?	Indicate if a Serious Adverse Event (SAE) form was sent to NCI concerning this event (Y for Yes or N for No). Such a form must be filed for an event that is serious as defined by ICH Guideline E6, or which the investigator considers very unusual and/or potentially serious. ICH Guideline E6 defines a SAE as an adverse drug experience, occurring at any dose, that is any of the following: • fatal; • immediately life threatening;

- results in inpatient hospitalization or prolongation of existing hospitalization;
- results in persistent or significant disability/incapacity; or
- results in a congenital anomaly/birth defect

Instructions for Completing Table 3: LISTING OF DEATHS

General:	Update this table on a monthly or quarterly basis. If information is unavailable, please use --- (dashes) for that particular box.
Patient ID	The study number for the patient, not their hospital record number.
Dose at Death	The dose of the study drug the patient was receiving at the time of death. The unit (e.g., mg) and frequency (e.g., bid) may be specified within the parentheses in the column header or within the table.
Date of Death	Specify date in Month/Day/Year format.
Cause of Death	Indicate the primary cause of death.
Relation to Drug	This is the principal investigator's assessment of the relationship between the death and the study drug. The following terms should be used: Unrelated, Unlikely, Possible, Probable, or Definite.

Attachment VII
NCI Common Toxicity Criteria

Attachment VIII
An Informed Consent Template

Investigator note:
This template will help you develop a consent document that meets both IRB and Federal requirements. Complete the requested information. Strive to explain this study as you would to an eighth grade student; use short sentences, avoid polysyllabic words, and define all medical terms. When the document is complete, delete all italicized and nonapplicable areas.

*Consent Version Date:*_____

Heading: Consent to Participate in a Research Study
TITLE OF STUDY:

INVESTIGATORS:
Principal Investigator:
Sub-Investigators (if applicable):

PURPOSE OF THE RESEARCH:
Investigator note: explain the study rationale (research problem) in layman terms.
You have been asked to take part in this study because...
This study will test...
This research will be done at _____ by Dr. _____.
(location) *(Principal Investigator)*

STUDY PROCEDURE(S):
If you choose to take part in the study, you will participate for _____
(length of time)
Investigator note:
- *list and explain ALL procedures the subject will undergo, when they will be done, and the total number of times performed.*
- *differentiate between investigational procedures and those performed as standard care.*
- *specify how subjects will take medication (times per day, dosage, and route), if applicable.*
- *list specimens to be collected, include frequency and amount.*
- *if specimens will be used for any purpose other than required by the protocol, the intended use must be disclosed.*

You cannot take part in this study if...
Investigator note: list absolute contraindications

During this study you will need to complete ...
Investigator note: list all paperwork (i.e., diaries, questionnaires), if applicable

*Subject Initials:*_____
Consent Version Date: _____

POTENTIAL RISKS:
The risks of taking part in this study are...
Investigator note: list the most serious and common risks of procedures, medications, etc. If applicable, include irreversibility of adverse reactions and how potential injuries will be minimized.

If you believe you are having a reaction in the study, you should call
_____ at _____.
(Principal Investigator) *(telephone number)*

If any new risks are found as the study continues, you will be notified.

POTENTIAL BENEFITS:
If you take part in the study, benefits include . . .
Investigator note: In addition to clinical benefits, free medication, procedures, etc. may be available.
The benefits to other subjects and society are (if applicable) . . .

ALTERNATIVE TREATMENTS:
Other treatments for _____ include . . .
You do not have to take part in an experimental program to receive treatment (*if applicable*).

CONFIDENTIALITY:
All your records will be kept confidential.
The only people that may review your records are . . .
Investigator note: Typically the sponsor, Institutional Review Board, and FDA may review the records.
If results of the study are presented or published, your name will not be used.

PAYMENT FOR STUDY:
You will receive no payment for the costs of procedures, tests or visits in connection with this research. Costs such as child care fees or missed time of work as a result of participating in this study may be incurred and these costs will not be covered directly. However, to help defray these costs, you will also receive a stipend of . . . *Investigator note: Specify exactly the amount to be given and how the funds will be distributed over the study period, if applicable.*

PAYMENT FOR INJURY:
_____ shall not provide compensation for medical expenses or any other compensation for research-related injuries. No other form of compensation is available. Compensation for lost wages and/or direct or indirect losses is not available. Further information about research-related injuries is available from the Office of the Institutional Review Board (_____).
telephone number

*Subject Initials:*_____
Consent Version Date: _____

RIGHT TO REFUSE OR WITHDRAW:
Your participation in this research is totally voluntary. You may withdraw at any time. Choosing not to take part, or leaving the study, will not affect the quality of your care. You will be informed of any new findings that may affect your willingness to participate. In some cases, such as when the study is not in your best interest, the doctor will take you out of the study.

QUESTIONS:
If you have any questions about the study, you should call _____
(Principal Investigator)
at _____.
(telephone number)

If you have any questions about your rights as a research subject, you should call
_____ at _____.
(IRB representative) *(telephone number)*

STATEMENT OF THE INVESTIGATOR
I have fully explained this study to the subject.

_____ _____
Signature of Investigator Date

STATEMENT OF THE SUBJECT
This study has been fully explained to me and I have been given the chance to ask questions. I want to volunteer for the study. I have been given a copy of this form.

_____ _____
Signature of Subject Date

_____ _____
Signature of Witness Date

*Subject Initials:*_____
Consent Version Date: _____

Informed Consent Form Checklist

Contract No._____ Investigator Name: _____
NCI Staff In Charge _____

	OK	COMMENTS
Investigator's Name		
IRB Protocol Number		
Purpose/Objectives		
Number of Participants		
Routine/Experimental Procedures		
Risks and Discomforts		
Pregnancy Statement		
Duration of Participation		
Benefits/New Findings Fee For Participation		
Alternative Procedures/Treatments		
Confidentiality		
Review of Records by FDA/NCI		
Liability:Emergency Care Injury Compensation		
Impartial Third Party		
Right to Withdraw		
Term w/ or w/out consent of subject		
Participation Voluntary		
Read before Signing (copy to subject)		
Signatures		